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ANTIBIOTIC DEVELOPMENT AND THEIR CHALLENGES

V. Evangeline Vinnarasi

PPG college of Pharmacy, Coimbatore, Tamil Nadu, India.

Corresponding Author Mail Id: evangeline1176@gmail.com

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ABSTRACT:

The development of antibiotics has been one of the most transformative advances in medical science, significantly it also reduces the mortality rate caused by bacterial infections. Since the discovery of penicillin in 1928, successive generation of antibiotics have been developed through both natural product discovery and synthetic chemistry. However, the rapid emergence of antibiotic -resistant pathogens poses a major global health threat, undermining current treatment regimens. Recent research has shifted towards novel approaches, including antimicrobial peptides, bacteriophage therapy and genome guided drug discovery. Moreover, advances in genomics, bioinformatics and high-throughput screening have revitalized the search for new antibiotics. This abstract outlines the historical evolution, current challenges and future directions in antibiotic development emphasizing the urgent need for innovation and global collaboration to combat antimicrobial resistance.

INTRODUCTION:

Antibiotics are powerful drugs that have revolutionized medicine by treating bacterial infections and enabling complex medical procedures. However, their widespread use has led to challenges such as antibiotic resistance, environmental contamination, and impacts on human and animal health. It works by targeting bacterial cell wall, protein synthesis, DNA replication or metabolic pathways. Resistance spreads rapidly, especially with overuse and misuse in medicine leads to multidrug-resistant pathogens. They are essential for treating infectious diseases and enable vital therapies and procedures. However, despite this success, their use continued use in 21st century is imperiled by two challenges. The first is that the microbes targeted by these drugs evolve antibiotics have drastically changed modern medicine and extended the average hu-

man resistance over time. The second is that antibiotic discovery and development are no longer cost effective using traditional reimbursement models. So, The future of antibiotics requires innovation in a field that has relied on highly traditional methods of discovery and development. It requires substantial changes in policy, quantitative understanding of societal value of these drugs, and investment in alternatives to traditional antibiotics.

HISTORICAL AND EVOLUTIONARY PERSPECTIVES

From penicillin to present: A historical review of antibiotic development:

The first antibiotic, salvarsan was deployed in 1910. In just over 100 years

man lifespan by 23 years. The discovery of penicillin in 1928 started the golden age of



natural product antibiotic discovery that peaked in the mid 1950s. Since then, a gradual decline in antibiotic discovery and development and evolution of drug resistance in many human pathogens has led to the current antimicrobial resistance crisis. In 1928, ALEXANDER FLEMING was the first to discover the antibacterial substances secreted by the penicillium mould and concentrate the active substance involved, giving it the name penicillin. His success in treating Harry Lambert's streptococcal meningitis, an infection until then fatal, proved to be a critical moment in the medical use of penicillin. Antibiotic resistance is now a major global health threat, with multidrug – resistance bacteria making infections harder and more expensive to treat. The pipeline for new antibiotics has dwindled due to scientific, economic, and regulatory barriers, with fewer companies investing in antibiotic research and development. Most current infections can still be treated, but clinical failures are increasing and some bacteria are resistant to nearly all available drugs. Future innovations include new technologies like genome mining, editing and advanced structural biology are enabling the discovery of novel antibiotics and drug targets. Alternative approaches include narrow-spectrum drugs, bacteriophages, monoclonal antibodies, vaccines and improved diagnosis.

GOLDEN AGE OF ANTIBIOTICS WHAT WE LEARNED AND WHAT WE LOST:

Historically, antibiotic discovery has been crucial in outpacing resistance and success is closely related to systemic procedures platform followed by the platforms of semi-synthesis and fully synthetic antibiotics. During 1940s to 1970s, it transformed medicine by drastically reducing the deaths from infectious disease and enabling modern medical procedures. The key ad-

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vantages are discovery of major antibiotic classes to treat diseases and increased life expectancy also enabled modern medicine and ensures safe surgery procedures, cancer and transplants. What we lost is that this overuse of antibiotics led to antibiotic resistance and decreases the effect of drug. Rising in antibiotic resistance threatens the advantages of procedures like surgeries, cancer treatments and organ transplants.

NATURAL AND SYNTHETIC ANTIBIOTIC, EVOLUTION OF DISCOVERY STRATEGIES:

Natural antibiotics were discovered by screening soil micro organisms especially actinomycetes. Synthetic antibiotics are laboratory designed drugs created to fight infections, especially those resistance to traditional treatments. New classes like iboxamycin have been developed to target multi resistance bacteria. Synthetic antibiotics can disrupt bacterial membranes, inhibit cell wall biosynthesis or interfere with essential proteins. Some synthetic antibiotics are effective against bacteria with resistance genes that render other drugs ineffective and certain designs show a low probability of resistance development due to poor bacterial penetration and lack of new classes. AI models including explainable deep learning are used to predict antibiotic activity, identify promising chemical structures and accelerate compound screening. But target based high throughput screening has limited success. Advances in genomics allow to identify biosynthetic gene clusters in both culturable and unculturable bacteria, revealing new potential antibiotics.

MECHANISTIC AND MOLECULAR INSIGHTS

MECHANISM OF ACTION AND RESISTANCE :-

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A molecular perspective on antibiotic evolution.

The gram-positive bacteria consists of cytoplasmic membrane surrounded by a tough rigid mesh called cell wall. In contrast, gram negative bacteria consists of thin cell wall that is surrounded by a lipid membrane known as outer membrane. The space between outer membrane and cytoplasmic membrane is known as periplasm. The outer membrane is a protective layer and prevents many substance from entering into the bacterium. However, this membrane contains channels called porins, which allows the entry of various molecules such as drugs. The cell wall is the tough layer that gives bacterium a characteristic shape and prevents it from osmotic and mechanical stresses. The cytoplasmic membrane prevents ions from flowing into or out of the cell and maintains the cytoplasmic and bacterial components in definite shape. The mechanism of antibiotics are classified based on their action. Inhibition of cell wall synthesis e.g. beta lactams. Disruption of protein synthesis e.g. tetracyclines and aminoglycosides. Interference with nucleic acid synthesis e.g. fluoroquinolones. Disruption of cell membrane integrity e.g. polymyxins. Inhibition of metabolic pathway e.g. sulfonamides.

MECHANISM OF ANTIMICROBIAL RESISTANCE:

Prevention of accumulation of antimicrobials either by decreasing uptake or increasing efflux of the antimicrobial from the cell i.e. changes in outer membrane permeability. Drug molecules to a cell can be transferred by diffusion through the bilayer and by self-uptake. The porin channels are located in outer membrane of gram-negative bacteria. The small hydrophilic molecules like beta lactams and quinolones can cross the outer membrane only through porins.

The decrease in number of porin channels lead to decrease in entry of beta lactam antibiotics and FQ into the cell, hence resistance to these classes of antibiotics. Acquired resistance to all the antibiotic classes in *Pseudomonas aeruginosa* to low outer membrane permeability. These includes enzymatic inactivation or modification of the antibiotics, alteration of antibiotic targets to reduce drug binding, reduced permeability or increased efflux to prevent antibiotic accumulation, bypass of metabolic pathways targeted by antibiotics, target protection where proteins shield the antibiotics target. Dual mechanism antibiotics and alternative therapies e.g. phage therapy and CRISPR based strategies are being explored to overcome resistance.

TARGETING THE BACTERIAL CELL WALL:**ADVANCES IN BETA-LACTAM AND GLYCOPEPTIDE ANTIBIOTICS**

It mainly focuses on structural and functional development of cell wall targeting drugs. Targeting the bacterial cell wall is a cornerstone of antibiotic therapy, as the cell wall is essential for bacterial survival and absent in human cells. This unique structure makes it an ideal target for both traditional and new anti-bacterial strategies, especially in facing of rising anti-biotic resistance. Key targets and its mechanism includes peptidoglycan biosynthesis, most antibiotics targeting the cell wall disrupt peptidoglycan synthesis, which is a critical component for bacteria rigidity and survival. Enzymes such as penicillin binding proteins are targets with beta-lactams and glycopeptides. Teichoic acids and other components includes in gram-positive bacteria, teichoic acids and related enzymes are also targeting for new drugs. Few agents includes like proteinaceous agents e.g. bacteriocins, phage lysins, and engineered pro-



teins are being developed to selectively disrupt bacterial cell walls offering alternatives to traditional small molecule antibiotics. Peptide antimicrobials include host defence peptides and bacteriocins can target various steps in cell wall synthesis providing new avenues for overcoming resistance. Chemical probes and imaging includes fluorescent and radiolabeled probes targeting cell wall components are advancing bacterial detection and infection imaging. But it also has some cons that is resistance mechanism where bacteria develop resistance through enzyme modification, efflux pumps and cell wall recycling, complicating therapy and necessitating new inhibitor strategies. The next is gram negative barriers the outer membrane of gram negative bacteria limits drug access making the cell wall targeting more challenging. Key challenges are to overcome resistance and addressing gram-negative barriers for future therapies.

RESISTANCE AND CHALLENGES:

ANTIBIOTIC RESISTANCE: DRIVERS, TRENDS AND GLOBAL HEALTH THREATS

Anti-biotic resistance is a rapidly escalating global health threat, undermining the effectiveness of treatments for bacterial infections and endangering public health worldwide. The rise of resistance bacteria is driven by complex, interconnected factors spanning human, animal and environmental domains and is projected to cause millions of deaths annually if not urgently addressed. Major causes of antibiotic resistance are

1. overuse and misuse:

Excess and inappropriate use of antibiotics in healthcare and animal husbandary

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is the primary driver, creating strong selective pressure for resistant strains.

2. Environmental spread:

Antibiotic residues and resistant bacteria enter the environment through waste water, agriculture and improper disposal, facilitating the spread of resistance gene.

3. Globalization:

Increased level, trade and migration accelerate the global dissemination of resistant bacteria.

4. Lack of new drugs:

Pharmaceutical investment in new antibiotic is lagging, leaving few options to combat emerging resistant pathogen.

A significant proportion of resistant genes confer resistance to multiple antibiotic classes, compounding the threat. Antibiotic use has surged globally, especially in low and middle income countries with consumption rates converging towards those in high income countries. Resistance rates are high in regions with high antibiotic use and poor regulation, but even countries with lower use face rising resistance due to global interconnections. Resistance threatens the safety of surgeries, cancer treatments and care for people. Antibiotic resistance infections cause higher rate of illness, death and healthcare costs with an estimated 4.95 million deaths in the year of 2019. Resistance could push millions into extreme poverty by 2030 due to increased healthcare costs and low productivity.

THE ANTIBIOTIC PIPELINE CRISIS: WHY ANTIBIOTICS AREN'T BEING DEVELOPED:

The development of new antibiotics has slowed dramatically in recent decades, despite the urgent need to combat rising anti-



biotic resistance. The main reason is economic developing antibiotic is expensive and offers poor financial returns, leading most large pharmaceutical companies to abandon in this area. Economic challenges are developing a new antibiotic can cost over 1 billion dollar but antibiotics are typically used for short courses and are often reserved to slow resistance, limiting sales and profits, this makes it hard for companies to recoup their investment, especially compared to drugs for chronic conditions or rare disease. Another challenge is that the traditional market driven models does not work for antibiotics. The need to limit use of new antibiotics (To preserve their effectiveness) further reduces potential revenue, discouraging investment. Scientific and technical factors includes most new antibiotics in development are modifications of existing drugs, with few truly novel classes reaching late stage trial tests. There have been advantages in understanding bacterial biology, genomics and new drug discovery methods.

ESKAPE pathogens and the antibiotic resistance challenge:

ESKAPE pathogens *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species are a major global health threat due to their ability to develop resistance to multiple antibiotics. The resistance limits treatment options, increased disease burden and raises mortality rates making the fight against these disease control. ESKAPE pathogens use diverse mechanisms to evade antibiotics, including producing enzymes that degrade drugs e.g beta lactamases altering drug targets increasing efflux pumps and forming biofilms that shield them from treatment. biofilm formation is especially important as it enhances survival and resistance, particularly against last resort anti-

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biotics. Resistance genes are often carried on mobile genetic elements, allowing rapid spread within and between species. Infections by ESKAPE pathogens are linked to higher morbidity, mortality and healthcare costs compared to infections by susceptible bacteria. Resistance rates have risen dramatically in recent years especially in countries with high antibiotic use and less stringent controls. New antibiotics and beta lactamase inhibitors have been introduced but resistance can develop rapidly even to drugs still in development. Combination therapies, alternative agents (e.g antimicrobial peptides, bacteriophages, plant derived compounds) and novel diagnostics i.e machine learning based nanosensors are being explored.

NOVEL APPROACHES AND FUTURE DIRECTIONS NEXT GENERATION ANTIBIOTICS:

The rise of antibiotic resistance bacteria has created an urgent need for next generation antibiotics. Traditional antibiotics are losing effectiveness and new approaches are being developed to address resistance improve specificity and reduce side effects. Next generation antibiotics aim to overcome the limitations of older drugs and offer hope in the fight against multidrug resistance. New antibiotics are being designed to target specific pathogens, reducing harm to beneficial microbiota and lowering the risk of resistance. Innovations include bacteriophage therapy, CRISPR case based antimicrobials and microbiome derived agents which can be programmed for greater precision and adaptability. Antimicrobial peptides are small proteins from various organisms that kill bacteria rapidly and less likely to induce resistance. They show promise against multidrug resistance strains and being optimised for clinical use though challenges like toxicity and stability remain. combining two antibiotics or an an-



tibiotic with an adjuvant such as efflux pump inhibitors can enhance effectiveness to overcome especially in gram negative bacteria. challenges includes toxicity and stability, regulatory and economic barriers, personalised and precision therapies.

ANTIBIOTICS IN THE AGE OF GENOMICS AND SYNTHETIC BIOLOGY:

Advances in genomics and synthetic biology are transforming how antibiotics are identified, engineered, and produced offering hope for overcoming current limitations and combating multidrug resistant pathogens. genome mining and sequencing have revealed a vast number of biosynthetic gene clusters in microbes, many of which encode for previously unknown or cryptic antibiotics. these tools allow researchers to predict, prioritize and activate new antibiotic pathways. Synthetic biology enables the design, construction and optimization of biological systems for antibiotic production. creating synthetic antimicrobial peptides and modifying existing antibiotic scaffolds to enhance activity and reduce resistance. Developing engineered probiotics and bacteriophages as novel therapeutic strategies. Integration of genomics, synthetic biology and chemical biology includes identification of essential bacterial targets, elucidates mechanisms of action and supports rational design of new antibiotics. This integrated approach is expanding chemical diversity and improving the chances of finding effective drugs against resistant bacteria.

PHAGE THERAPY :

phage therapy the use of bacteriophages to target and destroy bacteria is experiencing a resurgence as antibiotic resistance becomes a global health crisis. Beyond simply replacing replacing antibiotics, phage therapy is evolving with new scientific ad-

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vances, offering innovative approaches to infection control and even broader medical applications. Phages and viruses that specifically infect bacteria, making them highly targeted antibacterial agents. They can be used alone or in combination with antibiotics and are especially valuable for treating multidrug-resistant infections where other options have failed. Recent clinical success and ongoing trials highlight their potential but challenges remain in standardising dosing, delivery and regulatory approval. Phage-antibiotic combination enhance effectiveness and reduce resistance. Enzymes from phage can break down bacterial cell wall and biofilms offering new therapeutic tools. Phages are being explored for vaccine development, cancer therapy and as gene delivery vectors.

NANOTECHNOLOGY AND ANTIBIOTICS:

Nanotechnology is emerging as a powerful tool in the fight against antibiotic resistance, offering new ways to treat infections, enhance antibiotic effectiveness and even replace traditional antibiotics. By leveraging the unique properties of materials at the nanoscale, researchers are developing innovative strategies to address the growing threat of multidrug resistant bacteria. It provides direct antibacterial action such as silver, zinc oxide and other metals can kill bacteria through multiple mechanisms including disrupting cell membranes, generating reactive oxygen species and releasing metal ions. These multi-targeted actions make it bacteria to develop resistance. Penetrate and breakdown biofilms and making infections treatable. Nanocarriers improve the delivery stability and targeting of antibiotics, increasing their effectiveness and reducing their side effects. Additionally, nanotechnology is being explored for the delivery of antimicrobial peptides and the development of advanced diagnostic tools, fur-



ther broadening its impact in combating infections. While the potential is significant challenges remain regarding the safety, regulatory approval and large scale clinical application of these technologies.

CLINICAL AND REGULATORY PERSPECTIVES

CLINICAL TRIALS IN ANTIBIOTIC DEVELOPMENT:

Clinical trials are a critical step in development of new antibiotics, especially as resistance to existing drugs continues to rise. Most new antibiotics are evaluated in phase 2 and 3 clinical trials, often using non-inferiority designs, which aim to show that the new drug is not worse than existing treatments for common infections such as pneumonia, skin and soft tissue infections. These trials frequently do not include patients with infections caused by multi-drug -resistance organisms. The majority of recently approved antibiotics are modifications of existing drug classes rather than entirely new classes. Innovative trial designs, such as adaptive and organisms -specific trials are being proposed to better assess efficacy with patients with resistance infections. Preclinical, pharmacokinetic and pharmacodynamic studies and non-inferiority clinical trials play crucial roles in development of new antibacterial agents, with tetracyclines, carbapenems and cephalosporins.

ANTIBIOTIC STEWARDSHIP AND ITS ROLE IN DRUG DEVELOPMENT:

Antibiotic stewardship and drug development are critical strategies in fight against antibiotic resistance, a growing global health threat. Stewardship programs aim to optimize antibiotic use to preserve their effectiveness, while drug development seeks to introduce new antibiotics to address resistant infections. It has consistently

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shown to reduce inappropriate antibiotic use, lower rates of antibiotic-resistant infections and decreased healthcare costs in both hospital and community settings. Implementation of stewardship programs faces unique challenges in low and middle income countries, including limited diagnostic resources, regulatory gaps and the need for context specific interventions. It has been shown to reduce the incidence of multidrug-resistant organisms and *Clostridium difficile* infections. However, the reduction in antibiotic use can impact the market incentives for pharmaceutical companies to develop new antibiotics. The key outcomes are reduced antibiotic consumption, lower rates of resistance infections and improved patient outcomes.

THE ROLE OF MICROBIOTA IN ANTIBIOTIC EFFECTIVENESS AND RESISTANCE DEVELOPMENT:

The human microbiota, especially in the gut, plays a crucial role in both the effectiveness of antibiotics and the development of antibiotic resistance. Antibiotics can disrupt the balance of microbiota, reducing its ability to protect against pathogenic bacteria, a phenomenon known as colonization resistance, thereby increasing susceptibility to infections, including those caused by multidrug resistant organisms. The gut microbiota acts as a reservoir for antibiotic resistance genes. Overuse and misuse of antibiotics as well as environmental exposure, accelerate these processes, leading to long term health consequences and making infections hard to treat. Restoration of a healthy microbiota, through interventions such as fecal microbiota transplantation or next generation probiotics, is being explored as a strategy to re-establish colonization resistant pathogens, though these approaches require further refinement and standardisation.



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REPURPOSING EXISTING DRUGS AS ANTIBIOTICS:

Repurposing existing drugs as antibiotics is an increasingly important strategy to address the urgent threat of antimicrobial resistance, as it leverages the established safety profiles and pharmacological data of approved drugs to accelerate the development of new treatments for multidrug resistant bacteria. This approach has identified several non-antibiotic drugs such as anticancer, antipsychotic and antidiabetic agents that show antibacterial activity or can enhance the effect of traditional antibiotics sometimes disrupting bacterial biofilms or inhibiting resistance mechanisms. Combination therapies using repurposed drugs and conventional antibiotics can reduce required dosages, mitigate side effects and slow resistance development. Notable success includes the use of metformin as an adjuvant to boost the efficacy of antibiotics against pathogen. PROS include cost effective and faster clinical translation. CONS includes potential off-target effects, toxicity, regulatory hurdles and limited commercial incentives.

CONCLUSION:

The development of antibiotics represents significant achievements in medical history. Transforming once deadly infections into manageable conditions. Antibiotics have revolutionized in healthcare, saving millions of life and enabling complex medical condition and procedures. Despite the widespread has led to emergence of antibiotic resistance, causes a major global health threat. This challenges underscores the urgent need for responsible antibiotic use, ongoing research is going on into new antimicrobial agents and global cooperation to develop sustainable strategies. The future antibiotics depends on scientific innovation and also effective public health policies and global awareness.

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